Letter regarding article by Thijssen et al "Temporal and spatial variations in structural protein expression during the progression from stunned to hibernating myocardium" o Response

Correspondence

Letter Regarding Article by Thijssen et al, "Temporal and Spatial Variations in Structural Protein Expression During the Progression From Stunned to Hibernating Myocardium"

To the Editor:

It has been stated that glycogen accumulation and myofibrillar loss are specific pathognomonic histological abnormalities of hibernating myocardium.[1] We therefore read with great interest the study of Thijssen et al,[2] who reported that in a porcine model of hibernating myocardium histological findings of myofibrillar changes are global not regional, and therefore seem unlikely to be caused by chronic myocardial ischemia. These findings extend the experimental findings on glycogen content reported previously by the same group.[3] Thijssen et al[2] note that nearly all previous biopsy studies in humans have not used control samples from regions with normal contractile function within the same patient. The conclusions drawn in these reports may therefore be biased by differences in patient characteristics. Apart from the weaknesses in design as discussed by Thijssen et al, the conclusions on glycogen content in previous studies have limitations that weaken the conclusions on this other "hallmark" of hibernating myocardium. The semiquantitative periodic acid–Schiff staining method used in previous studies also stains nonglycogenic material. Furthermore, a considerable part of the glycogen pool may not be stainable by this method because it may be dissolved in the cytoplasm,[4] the increase in periodic acid-Schiff staining thus representing changes of the composition of the glycogen pool rather than an increase in the total glycogen pool. In a previous study of patients with heart failure, we quantified biopsy content of acid-extractable and protein-bound glycogen and related it to the content of noncollagen protein in hibernating regions. We observed that these contents were similar to control regions within the same patient.[5] These findings in humans and the experimental findings of Thijssen et al[2] and Thomas et al[3] question the generally accepted hypothesis of glycogen accumulation and myofibrillar loss as markers of metabolic derangement.[1] It seems that the prevailing conception that glycogen accumulation and myofibrillar loss are pathognomonic of hibernating myocardium[1] needs to be revised.

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Response

We thank Drs Wiggers and Bøtker for their interest in our study demonstrating that structural remodeling in cardiomyocytes occurs independently of chronic ischemia and most likely reflects a global response to chronic elevations in left ventricular preload. Wiggers and associates have previously described a similar observation with regard to metabolite storage and glycogen levels in patients with heart failure: As referred to in their letter, they observed equal levels of total glycogen content in normal and chronic reversibly dysfunctional myocardium.

The observations from both studies indicate a discrepancy between some of the previously defined characteristics of hibernation and chronic ischemia as being the supposed underlying trigger. In fact, besides our own observations and those of Wiggers et al, an increasing number of studies have reported a dissociation between cardiomyocyte remodeling and ischemia.[1–3] Thus, we support the view of Wiggers and Bøtker that the hibernating myocyte phenotype cannot be directly attributed to an adaptive response arising from regional alterations in myocardial perfusion, and that glycogen accumulation and myofibrillar loss are probably not pathognomonic of hibernating myocardium.

Myolysis, glycogen storage, and structural remodeling have been demonstrated at the structural and ultrastructural levels in a variety of different cardiac pathologies. It appears that this adaptive phenotype is a global response of the cardiomyocytes to cardiac stress, independent of regional flow reductions or ischemia. It remains unknown which triggers underlie this response, but we have shown that elevated preload may be involved.[4] This could also account for the "hibernating" phenotype of atrial cardiomyocytes during chronic atrial fibrillation.[5] The ultimate reversibility of this phenotype has not been clearly established other than in atrial fibrillation, in which it does not completely normalize.

Many new insights have emerged about the pathophysiology of viable chronically dysfunctional myocardium during the last several years, including the global nature of structural remodeling, transmural variations, reduced flow being a result rather than a cause, metabolic adaptation, and the importance of coronary flow reserve in the progression from stunning to hibernation. Insights from human studies are now complemented by chronic animal models that recapitulate most, if not all, of the features of human pathophysiology. We would applaud a critical revision and review of the criteria distinguishing the multiple pathophysiological entities underlying reversible contractile dysfunction with the recognition that the "hibernating cardiomyocyte" is a general adaptive cardiac phenotype to stress.

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